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09/640,530	08/17/2000	Michael P. DeNinno	PC10534AAD0	6169

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EXAMINER

CRANE, LAWRENCE E

ART UNIT PAPER NUMBER

1623

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5

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No. <b>09/640,530</b>	Applicant(s) <b>DeNinno et al.</b>	
	Examiner <b>L. E. Crane</b>	Group Art Unit <b>1623</b>	

**- THE MAILING DATE of this communication appears on the cover sheet beneath the correspondence address -**

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE **--03--** MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be filed after six months from the date of this communication.
- If the prior for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty days will be considered timely.
- If NO period for reply is specified above, such period shall, by default, expire SIX (6) MONTHS from the date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 USC §133).

## Status

- ☒ Responsive to communication(s) filed on **-08/17/00 (IDS) & 03/22/01(Supplemental IDS)-**.
- ☐ This action is **FINAL**.
- ☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

## Disposition of Claims

- ☒ Claims **---1-101---** are pending in the application. Claims **-[]-** have been cancelled. Of the above claims **---30-40 and 82-100---** are withdrawn from consideration.
- ☒ Claims **---41 and 45---** are allowed.
- ☒ Claims **---1-3, 10-12, 18-19, 22-28, 49, 50, 53 and 57-81---** are rejected.
- ☒ Claims **---4-9, 13-17, 20-21, 29, 42-44, 46-48, 51-52, 54-56 and 101---** are objected to.
- ☐ Claim(s) **---[]---** are subject to restriction or election requirement.

## Application Papers

- ☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
- ☐ The proposed drawing correction, filed on **-[]-** are ☐ approved ☐ disapproved.
- ☐ The drawing(s) filed on **-[]-** is/are objected to by the Examiner.
- ☐ The specification is objected to by the Examiner.
- ☐ The oath or declaration is objected to by the Examiner.

## Priority under 35 U.S.C. § 119(a)-(d)

- ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119 (a)-(d).
- ☐ All ☐ Some\* ☐ None of the CERTIFIED copies of the priority documents have been received.
- ☐ received in Application No. (Series Code/Serial Number) **-[]-**.
- ☐ received in the national stage application from the International Bureau (PCT Rule 17.2(a)).
- \* Certified copies not received: **-[]-**.

## Attachment(s)

- ☒ Information Disclosure Statement(s), PTO-1449, Paper No(s). **--02, 03--**
- ☒ Notice of Reference(s) Cited, PTO-892
- ☐ Notice of Draftsperson's Patent Drawing Review, PTO-948
- ☐ Interview Summary, PTO-413
- ☐ Notice of Informal Patent Application, PTO-152
- ☐ Other: **-[]-**

U.S. Patent Trademark Office

## Office Action Summary

PTO-326 (Rev. 06/19/01)  
S. N. **09/640,530**

Copy for ☒ **FILE** ☐ **APPLICANT**

Paper No. **05**

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No claims have been cancelled and no preliminary amendments filed as of the date of the instant Office action. Two Information Disclosure Statements (IDSs) filed August 17, 2000 and March 22, 2001 have been received with all cited references and made of record. An Associate  
5 Power of Attorney filed August 2, 2002 has been received and made of record.

The Abstract of the Disclosure is objected to because of excessive brevity and an incomplete sentence. Correction is required. See MPEP 608.01(b).

10 Applicant is reminded of the proper content of an Abstract of the Disclosure.

In chemical patent abstracts, compounds or compositions, the general nature of the compound or composition should be given as well as its use, e.g., "The compounds are of the class of alkyl benzene  
15 sulfonyl ureas, useful as oral anti-diabetics." Exemplification of a species could be illustrative of members of the class. For processes, the type reaction, reagents and process conditions should be stated, generally illustrated by a single example unless variations are necessary. Complete revision of the content of the abstract is required on a  
20 separate sheet.

Applicant is reminded of the proper language and format of an Abstract of the Disclosure.

The abstract should be in narrative form and generally limited to a single paragraph on a separate sheet within the range of 50 to 250  
25 words. It is important that the abstract not exceed 250 words in length since the space provided for the abstract on the computer tape used by

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the printer is limited. The form and legal phraseology often used in patent claims, such as "means" and "said," should be avoided. The abstract should describe the disclosure sufficiently to assist readers in deciding whether there is a need for consulting the full patent text for details.

The language should be clear and concise and should not repeat information given in the title. It should avoid using phrases which can be implied, such as, "The disclosure concerns," "The disclosure defined by this invention," "The disclosure describes," etc.

Claims 1-101 remain in the case.

Restriction to one of the following inventions is required under 35 U.S.C. §121:

I. Claims 1-29, 41-81 and 101, drawn to 2,N<sup>6</sup>-disubstituted-3'-deoxy-3'-aminoadenine ribouronic acids and ribouronamides, method of making, pharmaceutical compositions thereof, and a medicinal method of reducing tissue damage caused by ischemia and/or hypoxia, classified in Class 536, subclasses 027.110, 027.220 and 027.230 and Class 514, subclass 046.000.

II. Claims 30-32, drawn to 3-deoxy-3-amino-5-ribouronamide compounds, classified in Class 536, subclass 017.200.

III. Claims 33-36, drawn to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines, classified in Class 564, subclass 389.000.

IV. Claims 37-40, drawn to N<sup>6</sup>-substituted purines, classified in Class 544, subclass 262.000.

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V. Claims **82-87**, drawn to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is administered to  
5 reduce tissue damage caused by ischemia and/or hypoxia, classified in Class 514, subclass 046.000 and one or more other class/subclasses determined by the identity of the aldose reductase inhibitor.

VI. Claims **88-93**, drawn to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-  
10 ribouronic acid or -5-ribouronamide and a glycogen phosphorylase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia, classified in Class 514, subclass 046.000 and one or more other class/subclasses determined by the identity of the glycogen  
15 phosphorylase inhibitor.

VII. Claims **94-100**, drawn to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce  
20 tissue damage caused by ischemia and/or hypoxia, classified in Class 514, subclass 046.000 and one or more other class/subclasses determined by the identity of the cardiovascular agent.

The inventions are distinct, each from the other because of the following reasons:

25 Inventions **I and II** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or

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they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to purine ribonucleoside analogues and a medicinal methods of treating therewith, and the second invention being directed to 3-deoxy-  
5 3-aminoribouronamide compounds.

Inventions **I and III** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant  
10 case the inventions have different functions, the first invention being directed to purine ribonucleoside analogues and a medicinal methods of treating therewith, and the second invention being directed to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines.

Inventions **I and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they  
15 have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to purine ribonucleoside analogues and a medicinal methods of  
20 treating therewith, and the second invention being directed to N<sup>6</sup>-substituted purines.

Inventions **I and V** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or  
25 they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to purine ribonucleoside analogues and a medicinal methods of treating therewith, and the second invention being

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5 directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

10 Inventions **I and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to purine ribonucleoside analogues and a medicinal methods of treating therewith, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a glycogen phosphorylase inhibitor, and methods of  
15 treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

20 Inventions **I and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different modes of operation, the first invention being directed to purine ribonucleoside analogues and a medicinal methods of treating therewith, and the second invention being  
25 directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

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Inventions **II and III** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the  
5 instant case the inventions have different functions, the first invention being directed to 3-deoxy-3-aminoribouronamide compounds, and the second invention being directed to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines.

Inventions **II and IV** are unrelated. Inventions are unrelated if it  
10 can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions, the first invention being directed to 3-deoxy-3-aminoribouronamide compounds, and the  
15 second invention being directed to N<sup>6</sup>-substituted purines.

Inventions **II and V** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant  
20 case the inventions have different functions and different modes of operation, the first invention being directed to 3-deoxy-3-aminoribouronamide compounds, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribose acid or -5-  
25 ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.



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Inventions **II and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the  
5 instant case the inventions have different functions and different modes of operation, the first invention being directed to 3-deoxy-3-aminoribouronamide compounds, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-  
10 ribouronamide and a glycogen phosphorylase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **II and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or  
15 they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and different modes of operation, the first invention being directed to 3-deoxy-3-aminoribouronamide compounds, and the second invention being  
20 directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

25 Inventions **III and IV** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the

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instant case the inventions have different functions, the first invention being directed to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines, and the second invention being directed to N<sup>6</sup>-substituted purines.

5           Inventions **III and V** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the  
10           instant case the inventions have different functions and/or different modes of operations, the first invention being directed to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-  
15           ribouronic acid or -5-ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

          Inventions **III and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions,  
20           or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and/or different modes of operation, the first invention being directed to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines, and the second invention being directed to pharmaceutical compositions and kits  
25           comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a glycogen phosphorylase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

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Inventions **III and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and/or different modes of operation, the first invention being directed to N,N-phthalimido derivatives of 2,5-(disubstituted)benzylamines, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **IV and V** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and/or different modes of operation, the first invention being directed to N<sup>6</sup>-substituted purines, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **IV and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the

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instant case the inventions have different functions and/or different modes of operation, the first invention being directed to N<sup>6</sup>-substituted purines, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a glycogen phosphorylase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **IV and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and/or different modes of operation, the first invention being directed to N<sup>6</sup>-substituted purines, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **V and VI** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and different modes of operation, the first invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is

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administered to reduce tissue damage caused by ischemia and/or hypoxia, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a glycogen phosphorylase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **V and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and different modes of operation, the first invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and an aldose reductase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Inventions **VI and VII** are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together, or they have different modes of operation, or they have different functions, or they have different effects. (MPEP §§ 806.04 & 808.01). In the instant case the inventions have different functions and different modes of operation, the first invention being directed to pharmaceutical

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compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a glycogen phosphorylase inhibitor, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia, and the second invention being directed to pharmaceutical compositions and kits comprising a 1([2,N<sup>6</sup>-disubstituted]-adenin-9-yl)-3-deoxy-3-amino-5-ribouronic acid or -5-ribouronamide and a cardiovascular agent, and methods of treating wherein said composition is administered to reduce tissue damage caused by ischemia and/or hypoxia.

Because these inventions are distinct for the reasons given above and 1) have acquired a separate status in the art as shown by their divergent classification, 2) have acquired a separate status in the art because of their recognized divergent subject matter, and 3) the search required for any one of Groups **I-VII** is not required for any one of the other Groups, restriction for examination purposes as indicated is proper.

During a telephone conversation with Ms. Arlene K. Musser on August 2, 2002 a provisional election was made with traverse to prosecute the invention of Group **I**, claims **1-29, 41-81 and 101**. Affirmation of this election must be made by applicant in responding to this Office action. Claims **30-40 and 82-100** are withdrawn from further consideration by the Examiner, 37 C.F.R. §1.142(b), as being drawn to a non-elected invention.

Applicant is advised that the response to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 C.F.R. §1.143).

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Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 C.F.R. §1.48(b) if one or more of the currently named inventors is no longer an inventor if at least one claim remaining in the application.

- 5 Any amendment of inventorship must be accompanied by a diligently-filed petition under 37 C.F.R. §1.48(b) and by the fee required under 37 C.F.R. §1.17(h).

Claims **1-29, 41-81 and 101** remain under examination in the case.

- 10 The disclosure is objected to because of the following informalities:

At page 74 at line 7, the acronym "SDH" is used but has not been defined. Applicant is respectfully requested to provide a definition, preferably by adding a prior art reference which defines same.

Appropriate correction is required.

- 15 Claims **2-29, 42-44, 46-48, 49, 50-56, 58-81 and 101** are objected to because of the following informalities:

At line 1 of each of claims **2-29, 42-44, 46-48, 50-56 and 58-81**, the term "A" must be replaced by the term -- The --.

- 20 In claim **49** at line 7, inappropriate terminal punctuation appears at the end of the noted line.

In claim **101** the individual chemical names are not clearly separated by either punctuation or spacing. Examiner suggests semicolons (-- ; --) in place of the commas presently separating the

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names. In addition claim 101 lacks the term -- and -- at the end of line 8, an addition required to make the Markush group format complete.

Appropriate correction is required.

5 Claims 1-3, 10-12, 18-19, 22-27 and 57-81 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

10 The instant claims have not met the written description standard of Regents of the University of California v. Eli Lilly (119F.3d 1559 at 1568; 43 USPQ2d 1398 at 1406 (Fed. Cir 1997)); see MPEP §2163 at page 2100-162, column 1. Applicant is requested to note that the examples of the instant disclosure are limited to 3-deoxy-3-aminoribouronic acid and amide compounds, and does not describe any other 5-functionality in  
15 place of carboxyl or carboxamide or any alternative membered ring in place of ribofuranosyl. Therefore, the noted claims are deemed to lack adequate written description in support of the full scope of embodiments of the instant noted claims. The same argument applies to the excessive breadth of the definitions of variables G, R<sup>4</sup>, and  
20 " R<sup>4</sup> and R<sup>5</sup> " taken together.

Claims 1-3, 10-11, 18-19 and 57-81 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly  
25 connected, to make and/or use the invention.

In claims 1-3, 10-11 and 18-19 variable R<sup>1</sup> is lacking proper supporting enabling disclosure with only compounds having



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“hydroxymethyl,” “carboxyl,” various “alkoxycarbonyl,” and  
“aminocarbonyl” groups supported by a plethora of prior art  
embodiments or by instant specific embodiments, or both. Applicant is  
referred to **Crane et al.** (PTO-892 ref. T) at page 285, lines 12-14,  
5 wherein a neighboring group effect between the protonated N-3 and  
glycosyl oxygens of a C-nucleoside is disclosed. Examiner recalls this  
subject matter from his Ph.D. thesis research and further recalls that the  
thesis describes in some detail how the  $\text{CH}_3\text{-S-C=N(H}^+\text{)-}$  could be  
positioned so that the protonated nitrogen could be transferred to an  
10 oxygen on the adjacent benzylidenyl ring to accelerate benzylidene  
group removal when the electron donating ability of the methylthio  
group was available to enhance the basicity of the N-3 nitrogen. In light  
of this neighboring group effect in a closely analogous structure and the  
well known sensitivity of 2-unsubstituted purines to “covalent  
15 hydration,” examiner questions the ability of applicant to actually make  
claimed compounds wherein highly nucleophilic “aminoiminomethyl”  
groups (“-C(=NH)-NH<sub>2</sub> ?? aka “amidine” ??) are present at the 5'-location  
of the ribofuranosyl substituent group. Examiner wonders whether such  
a highly basic and nucleophilic group in close proximity to a purine ring  
20 C-2 would not cause spontaneous ring opening of the adjacent  
pyrimidine ring. Applicant is invited to show that such compounds may  
be synthesized, or alternatively is invited to delete the noted terms from  
the instant claims.

Also examiner questions the term “carbamoyl” because, whether the  
25 “O” or “N” atom of this group (O-carbamoyl =  $\text{H}_2\text{N-C(=O)-O-}$  ) is  
attached to the ribofuran ring, the implication is that applicant has  
prepared an “erythrofuranoose” derivative, a species the synthesis of  
which is clearly not enabled by the instant specification.

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Claims 1-3, 10-12, 18-19, 22-27 and 57-81 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most  
5 nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in *In re Wands* (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination  
10 of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is excessive, specifically because of the presence in claims 1-3, 10-12, 18-19 and 22-27 of the definitions of variables X, Z, R<sup>1</sup>, G, R<sup>4</sup>, R<sup>4</sup> and R<sup>5</sup> taken together, the presence in claims  
15 71-75 and 79 of the terms "prophylactically," "prior to," "perioperative" and "prevent," and the total absence of any test data in support of method claims 57-81.

B. The nature of the invention is directed to analogues of purine nucleosides, pharmaceutical compositions thereof, final steps in the  
20 process of making said analogues, and a method of reducing tissue damage caused by ischemia or hypoxia by administration of said analogues to a host in need thereof.

C. The state of the prior art is well developed. There are numerous other closely related purine nucleoside analogues which are known in  
25 the art to mimic the capability of adenosine to limit the deleterious effects of ischemia or hypoxia.

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D. The level of one or ordinary skill is high, an understanding of organic synthesis of nucleosides, and the pharmacology of adenosine analogs being required to practice the instant claimed invention.

5 E. The level of predictability in the art is fairly high in the treatment of whole living hosts, there being numerous examples in the prior art wherein adenosine and analogues thereof (NECA, etc.) have been used to assist in the mitigation of tissue damages known to result from ischemia and/or hypoxia, e.g. in hearts and other organs in the process of transport between hosts. However, the minimization of damage caused  
10 by ischemia/hypoxia in living tissue during storage and/or transport between living hosts (transplantable organs, etc.) is much less well understood and therefore much less predictable.

F. The amount of direction provided by the inventor includes detailed directions for the synthesis of a substantial list of potential  
15 active ingredients, but fails to provide a single example wherein actual testing has substantiated the alleged pharmacological activity of any single compound synthesized.

G. The existence of working examples is limited to chemical synthesis of potential active ingredients.

20 H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure is de minimus concerning the chemical synthesis of the specific embodiments, but increases to an unacceptable level when the un-enabled variables and/or un-enabled the additional layers upon layers of substitution found in the  
25 definitions X, Z, R<sup>1</sup>, G, R<sup>4</sup>, R<sup>4</sup> and R<sup>5</sup> taken together are considered. Attention is drawn in particular to the laundry lists of substituents within the definitions of variables R<sup>1</sup>, G, R<sup>4</sup> and R<sup>4</sup> and R<sup>5</sup> taken

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together, wherein nearly all of these listed substituents have not been enabled by even a single embodiment. In addition, the total absence of any test data to establish that the instant claimed compounds are predictably active in line with the content of the prior art means that the claims directed to methods of treating and pharmaceutical compositions are entirely lacking in enabling support, whether the method is applied to a host already suffering from ischemia/hypoxia or is treated prophylactically in anticipation thereof.

Claims 1-3, 10-12, 18-19, 24-28, 49, 50, 53, 71-75, 79 and 81 are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claim 1 at line 29, the definition of  $R^4$  as "a bond" renders the definition incomplete because there is no portion of the noted claim wherein the substituent bonded at position  $R^4$  when  $R^4$  is a bond has been defined. The same criticism applies to variable  $R^5$ .

In claim 1 at line 31, the term "optionally linked through ( $C_1$ - $C_3$ )alkyl" is unclear because the claim has not defined what atom of the previous listed "ring" substituent is being linked to what other atom of said "ring" substituent or to what atom of Formula I. For examples of the same or a very similar problem see also claim 1 at lines 33-34, at line 53, and at lines 56-57, claim 10 at line 23, claim 11 at line 17, claim 12 at line 9, claim 18 at line 13, claim 19 at line 8, claim 24 at line 15 and lines 18-19, claim 25 at line 14, claim 26 at line 20, claim 27 at line 9, and claim 28 at line 5.

In claim 1 the definition of variable " $R^4$  and  $R^5$  taken together" includes the term "said ring ... optionally having one to three

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heteroatoms." The noted term is directed to rings wherein a nitrogen is always found between R<sup>4</sup> and R<sup>5</sup> (see the definition of variable G) and therefore the noted term is incorrect in its implication that R<sup>4</sup> and R<sup>5</sup> can be in a ring with no hetero atoms (the presence of one heteroatom is required, and therefore cannot be "optional").

In claims 1-3, 10-11 and 18-19 the terms "carbamoyl," "alkyl carbamoyl," and "methylcarbamoyl" are both incomplete and indefinite. The functional group "O-carbamoyl" is -- H<sub>2</sub>N-C(=O)-O- --. Carbamoyl may be attached to another molecule by either nitrogen or one of the oxygen substituents, but if attachment is through nitrogen, then the oxygen must be alkylated or arylated, or otherwise substituted in order for the resultant structure to be stable (carbon dioxide easily produced otherwise). The noted terms fail to specify which atom (O or N) is attached to the ribofuranose ring at the R<sup>1</sup> substituent location, and also how the other atom is substituted, thereby rendering the noted terms incomplete.

Claim 49 at line 7, the term "acylating" is incomplete because said claim fails to provide any reagent to effect the process claimed.

Claim 50 lacks proper antecedent basis in claim 49 because claim 49 does not provide for any intermediate "esterification" step. Applicant may elect to introduce the term -- further comprising -- into this claim to effectively address this rejection.

In claim 50 at line 4, the term "esterified" is incomplete because said claim fails to provide any reagent to effect the process claimed.

Claim 53 is technically incorrect in its representation of temperature scale (both occurrences). The abbreviation for temperatures in "Centigrade" is upper case -- C --.

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5 In claims **71-75 and 79** the terms "prophylactically," "prior to," "perioperative" and "prevent" imply prospective treatment of a well host, and therefore to subject matter not included within the meaning of claim **57**, and thereby render the instant claims lacking in proper antecedent basis.

10 In claim **81**, the term "for the reduction of tissue damage resulting from ischemia or hypoxia" is superfluous because this limitation fails to further limit the scope of a pharmaceutical composition claim wherein patentable weight is limited to the identity of the active ingredient(s) and carrier(s) and proportions thereof only. If applicant elects to delete said term, said claim will become equivalent to claim **80** and is therefore subject to cancellation as a duplicate.

15 Review of the submitted and discovered prior art now of record has failed to produce a single reference or combination of references usable in an anticipation or obviousness rejection.

Claims **41 and 45** are allowable as submitted.

20 Claims **4-9, 13-17, 20-21, 29, 42-44, 46-48, 51-52, 54-56 and 101** are objected as containing formal errors and/or as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims, and/or corrected to eliminate formal errors.

25 Claims **1-3, 10-12, 18-19, 22-28, 49, 50, 53 and 57-81** would be allowable if rewritten or amended to overcome the noted objections and the rejections under 35 U.S.C. §112.

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This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any  
5 evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. §1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(f) or (g) prior art under 35  
10 U.S.C. §103(a).

Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone numbers for the FAX machines  
15 operated by Group 1600 are (703) 308-4556 and 703-305-3592.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is 703-308-4639. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through  
20 Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O, Wilson, can be reached at (703)-308-4624.

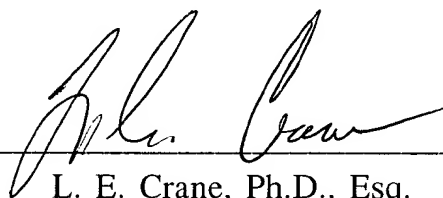
Any inquiry of a general nature or relating to the status of this  
25 application should be directed to the Group 1600 receptionist whose telephone number is 703-308-1235.

Serial No. 09/640,530

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LECrane:lec  
09/26/03

A handwritten signature in cursive script, appearing to read "L. E. Crane", is written over a horizontal line.

L. E. Crane, Ph.D., Esq.

Patent Examiner

Technology Center 1600

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